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Effect of 6% Hydroxyethyl Starch 130/0.4 as a Priming Solution on Coagulation and Inflammation Following Complex Heart Surgery

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Purpose: Prolonged duration of cardiopulmonary bypass aggravates the degree of inflammation and coagulopathy. We investigated the influence of 6% hydroxyethyl starch (HES) 130/0.4 on coagulation and inflammation compared with albumin when used for both cardiopulmonary bypass priming and perioperative fluid therapy in patients undergoing complex valvular heart surgery. **Materials and Methods:** Fifty four patients were randomly allocated into albumin-HES, albumin-nonHES, and HES-HES groups. The cardiopulmonary bypass circuit was primed with 5% albumin in the albumin-HES and albumin-nonHES group, and with HES in the HES-HES group. As perioperative fluid, only plasmalyte was used in the albumin-nonHES group whereas HES was used up to 20 mL/kg in the albumin-HES and albumin-HES group. Serial assessments of coagulation profiles using the rotational thromboelastometry and inflammatory markers (tissue necrosis factor-α, interleukin-6, and interleukin-8) were performed. **Results:** Patients' characteristics and the duration of cardiopulmonary bypass (albumin-HES; 137±34 min, HES-HES; 136±47 min, albumin-nonHES; 132±39 min) were all similar among the groups. Postoperative coagulation profiles demonstrated sporadic increases in clot formation time and coagulation time, without any differences in the actual amount of perioperative bleeding and transfusion requirements among the groups. Also, inflammatory markers showed significant activation after cardiopulmonary bypass without any differences among the groups. **Conclusion:** Even in the presence of prolonged duration of cardiopulmonary bypass, HES seemed to yield similar influence on the ensuing coagulopathy and inflammatory response when used for priming and perioperative fluid therapy following complex valvular heart surgery compared with conventional fluid regimen including albumin and plasmalyte.

Key Words: Blood coagulation, inflammation, cardiopulmonary bypass, cardiac surgical procedures

INTRODUCTION

To prime the cardiopulmonary bypass (CPB) circuit, various colloids are com-

monly used in addition to crystalloids in order to maintain the oncotic pressure and reduce fluid retention after CPB.[1,2] Among them, human albumin may be advantageous as it preserves the coagulation system[3] and reduces inflammatory response.[4,5] However, its cost and potential to transmit infection limit the more widespread use of albumin.[6]

Six percent hydroxyethyl starch (HES) 130/0.4 (6% Voluven Inj., Fresenius Kabi, Germany) is a synthetic colloid that has the advantage of a stronger plasma-expanding effect, an infrequent incidence of allergic reaction, and lower cost compared with albumin.[7,8] As with other colloids, HES can produce dilutional coagulopathy and decrease factor VIII and von Willebrand factor levels. HES can also reduce the accessibility of glycoprotein IIb/IIIa on the surface of platelets. Nonetheless, due to a lower molecular weight and molar substitution ratio than its congeners, 6% HES 130/0.4 has been shown to retain plasma-expanding effects with minimal influence on coagulation and higher plasma clearance.[9] In conjunction, HES 130/0.4 has been safely used in the cardiac surgical setting, even when used as a component of the priming solution, without causing clinically significant coagulopathy.[9]

Inflammation is known to induce coagulopathy with a simultaneous suppression of the fibrinolytic system.[10] In cases of complex valvular heart surgery requiring prolonged duration of CPB, the negative influence of CPB-induced inflammation on the coagulation system is likely to be accentuated resulting in a clinically significant coagulopathy, that may also be affected by the type of colloids used as a priming solution and/or perioperative fluid. Heretofore, the efficacy of 6% HES 130/0.4 under these circumstances has not been validated.

In this randomised and controlled study, we compared the effects of 6% HES 130/0.4 with human albumin on coagulation by using rotational thromboelastometry (ROTEM), and their effects on inflammation when used perioperatively as a component of the priming solution in patients undergoing complex valvular heart surgery.

MATERIALS AND METHODS

After Institutional Review Board approval and informed consent was obtained, 54 patients scheduled for complex cardiac surgery (combined mitral valve surgery and tricuspid annuloplasty, double-valve surgery, combined aortic valve replacement and ascending aorta replacement, Bentall's operation, combined valve and coronary artery bypass graft surgery or redo surgery) at the Cardiovascular Hospital of the Yonsei University Health System between June 2009 and January 2011 were prospectively enrolled. Patients who had received heparin, Coumadin, or antiplatelet drugs within 5 days before surgery were excluded from the study.

A computerized randomization table was used to assign the patients to one of the three groups (albumin-HES, HES-HES, or albumin-nonHES) according to the priming solution preparation and perioperative fluid management strategies. Regarding the priming solution, the CPB circuit was primed with 500 mL of 5% albumin and 1000 mL of plasmalyte solution (Plasma Solution A Inj., CJ Pharma, Seoul, Korea) in the albumin-HES and albumin-nonHES group. In the HES-HES group, the circuit was primed with 500 mL 6% HES 130/0.4 and 1000 mL of plasmalyte solution. Heparin (10 mg/L), sodium bicarbonate (40 mEq) and 20% mannitol (5 mL/kg) were added to the priming solution. A perfusionist who was not involved in the study prepared the priming solutions, and physicians were blinded to the randomization results. Regarding the fluid management, in the albumin-HES and HES-HES group, up to 20 mL/kg of 6% HES 130/0.4 per day (including the volume used for priming) and plasmalyte solution were infused throughout the study period. In the albumin-nonHES group, only plasmalyte solution was infused. The infusion rate was adjusted to maintain the left ventricular end diastolic area, which was monitored with transesophageal echocardiography, within 20% of the baseline, and to keep the cardiac index above 2.0 L/min/m^2 and urine output at more than 0.5 mL/kg/h during the surgery.

A standardized anesthetic and CPB management was provided to all patients. Anesthesia was induced with intravenous midazolam (0.03-0.05 mg/kg), sufentanil (1.5-2 mcg/kg) and rocuronium (50 mg). Anesthesia was maintained with a continuous infusion of sufentanil (0.2-0.3 mcg/kg/h), vecuronium (1-2 mcg/kg/min), and sevoflurane (0.6-2.0%) in 50% oxygen with air. Norepinephrine was infused when the mean arterial pressure fell below 60 mm Hg. When the norepinephrine dose exceeded 0.3 μg/kg/min, vasopressin was added. Indications of milrinone infusion was when the cardiac index was below <2.0 L/min/m^2 or when mixed venous oxygen saturation was below 60% despite optimization of preload and hematocrit.

All patients were anticoagulated with heparin 300 units/kg before CPB was established. Activated clotting time was measured every 30 min and kept above 480 sec during CPB

with additional doses of heparin if required. CPB was performed with non-pulsatile flow (2.2-2.4 L/min/m^2) under α-stat management. Ultrafiltration was performed in all patients during CPB. To maintain the filling volume of the reservoir, plasmalyte solution was added. Packed red blood cells (pRBC) were added only when the patients' hematocrit was less than 20% during CPB. Moderate hypothermia (33-34°C) and cold blood cardioplegia were used in all cases. After CPB was terminated, heparin was neutralized with 1 mg of protamine for each 100 units of the initial dose of heparin. Additional doses of protamine were given to achieve the pre-bypass activated clotting time. Additionally, blood from the CPB circuit was salvaged with a cell salvage device (Cell saver®, Haemonetic Corp, Braintree, MA, USA) and retransfused after sternal closure. After surgery, all patients were transferred to the intensive care unit (ICU), where pRBC were transfused when hematocrit was lower than 25%. Fresh frozen plasma (FFP) was transfused when the international normalized ratio was above 1.5 with bleeding greater than 200 mL/h for 2 consecutive hours after operation. Platelet concentrates were transfused when a platelet count was less than 50000/μL with excessive bleeding greater than 200 mL/h for 2 consecutive hours after operation. Surgical re-exploration was indicated when bleeding was >200 mL/h for 6 consecutive hours or >400 mL during the first hour postoperatively, despite a normal active clotting time (ACT) and global coagulation status.

Cardiac index, heart rate, mean arterial blood pressure, central venous pressure, pulmonary arterial pressure, and pulmonary artery occlusion pressure were checked 10 min after induction, 10 min after weaning from CPB, 10 min after pericardial closure, and 1 h, 12 h, and 24 h after the operation. In the postoperative period, the incidence of acute kidney injury according to the risk, injury, failure, loss and end-stage kidney (RIFLE) criteria,[11] the length of stay in the ICU, and length of postoperative hospitalization were also recorded. Physicians who were blinded to the studies directed postoperative management and collected data for all the patients.

Rotational thromboelastometry (ROTEM®, PentapharmGmBh, Munich, Germany) tracing

Blood samples for ROTEM tracing were obtained via a radial artery catheter into polypropylene tubes (BD Vacutainer®, BD Diagnostics, Plymouth, UK) containing 3.2% buffered citrate before and 24 h after CPB. ROTEM using 3 activators [intrinsic ROTEM (InTEM®); extrinsic ROTEM (ExTEM®); and fibrinogen ROTEM (FibTEM®)] was performed by the same investigator who was unaware of the group assignment. The measured ROTEM variables were: coagulation time, clot formation time, α angle, and maximum clot firmness. Coagulation time represents the onset of coagulation, whereas the clot formation time and α-angle represent the initial rate of fibrin polymerization. Maximum clot firmness is a measurement of the maximal viscoelastic strength of the clot. ExTEM (tissue factor reagent) and InTEM (ellagic acid reagent) tests are indicated to evaluate platelet, plasma factor, and heparin. FibTEM (modified ExTEM test with cytochalasin D) is indicated to evaluate fibrinogen. Combination of ExTEM and FibTEM allows differential diagnosis of thrombocytopenia and/or hypofibrinogenemia within 20 min.[12]

Hemostatic variables

Hematocrit, platelet count, prothrombin time and activated partial thromboplastin time were measured before and 24 h after CPB. During the intraoperative period and postoperative 24 h in the ICU, the amount of blood loss, urine output, fluid administered, and transfusion requirements were recorded. Intraoperative blood loss was recorded as the amount of reinfused salvaged blood by the cell salvage device. Postoperative blood loss was recorded as the volume of chest tube drainage measured at 24 h after operation, which was not reinfused.

Inflammatory markers

Blood samples for interleukin (IL)-6, IL-8, and tumor necrosis factor (TNF)-α were obtained from arterial blood before and 4, 12, and 24 h after CPB. The samples were placed in ice after collection and centrifuged immediately. Afterwards, the serum was separated and stored frozen at -70°C. Serum concentrations of TNF-α, IL-6, and IL-8 were assayed using enzyme-linked immunosorbent assay (Quantikine® high-sensitive immunoassay; R&D Systems, Minneapolis, MN, USA). The assay has a detection limit of 0.038, 0.016, and 1.5 pg/mL for TNF-α, IL-6, and IL-8, respectively.

Statistical analysis

On the basis of an expected difference in postoperative maximum clot firmness according to a previous study,[13] a sample size of 18 in each group was determined with a two-sided α level of 0.05 and a power of 0.8.

Statistical analyses were performed with SPSS 15.0 (SPSS Inc., Chicago, IL, USA). Normality of distribution was assessed with q-q plot and the Shapiro-Wilk test. Parametric data were analyzed using the analysis of variance for re-

peated measurements followed by post hoc Dunnett's test. Non-parametric data were compared using the Kruskall-Wallis and Friedman tests among and within the groups, respectively. After the Kruskall-Wallis test, the Mann-Whitney U test was applied to analyze difference between the two groups. The Wilcoxon test was used for paired comparisons. Frequencies were evaluated by chi-squared test and Fisher's exact test. All values were expressed as median [interquartile range], mean±standard deviation, or the number of patients. In figures, inflammatory cytokines were expressed as median (min, max). A p-value of <0.05 was considered to be statistically significant.

RESULTS

Patients' characteristics, EuroSCORE, and operative data including the duration of CPB and the amount of ultrafiltration during CPB were all similar among the groups (Table 1).

There were no significant differences in the perioperative hemodynamic variables among the groups throughout the study period. In all groups, mean pulmonary arterial pressure up to 24 h after the surgery was significantly decreased compared to each corresponding baseline value (data not shown).

ROTEM variables were similar among the groups before and after CPB (Table 2). InTEM, clot formation time increased after CPB in the albumin-HES and albumin-non-HES group. Furthermore, maximum clot firmness inTEM decreased significantly in all groups after CPB. In the albumin-non HES group, ExTEM clot formation time increased and maximum clot firmness reduced, and FibTEM coagulation time increased significantly after CPB. In the albumin-HES and HES-HES groups, ExTEM and FibTEM variables remained unchanged after CPB (Table 2).

Perioperative hematologic variables, including the routine coagulation tests, the actual amount of bleeding, and transfusion requirements, were all comparable among the groups. Perioperative fluid balance was also similar among the groups with no patients requiring hemostatic re-exploration (Table 3).

Postoperative data, including the incidence of acute kidney injury, lengths of stay in the ICU and hospital, and mortality rate, were all similar among the groups (Table 4). No patients required postoperative renal replacement therapy.

Table 1. Patients' Characteristics

	HA-HES group (n=18)	HES-HES group (n=18)	HA-nonHES group (n=18)	p value
Age (yrs)	62±11	64±13	57±17	0.324
Gender (male/female)	6/12	7/11	7/11	0.923
BMI (kg/m^2)	23.4±3.0	23.7±3.9	22.6±3.4	0.652
Diabetes mellitus (n)	2	3	2	1.000
Hypertension (n)	5	7	5	1.000
Pre-operative LVEF (%)	67±7	56±15	61±16	0.068
Preoperative medications (n)				
β-blockers	4	5	3	0.624
Calcium channel blockers	4	4	3	0.682
Renin angiotensin system inhibitors	6	9	8	0.504
Digoxin	5	4	8	0.336
Diuretics	10	12	13	0.300
Type of surgical procedures (n)				0.110
MVR+TAP	5	2	4	
DVR	6	3	6	
AVR+ascending aorta replacement	4	8	3	
Bentall's operation	2	2	3	
Valve+CABG	1	3	2	
Redo operation	2	4	2	0.516
EuroSCORE	2 [1-5]	3 [2-4]	2 [1-3]	0.403
Duration of ACC (min)	110±26	104±44	100±32	0.681
Duration of CPB (min)	137±34	136±47	132±39	0.918

HA, 5% human albumin; HES, 6% hydroxyethyl starch 130/0.4; BMI, body mass index; LVEF, left ventricular ejection fraction; EuroSCORE, European System for Cardiac Operative Risk Evaluation; AVR, aortic valve replacement; MVR, mitral valve replacement; TAP, tricuspid annuloplasty; DVR, double valve replacement; CABG, coronary artery bypass graft; ACC, aortic cross clamp; CPB, cardiopulmonary bypass.
Values are number of patients or mean±standard deviation or median [interquartile range].

Table 2. ROTEM before [Pre] and 24 h after [Post] CPB

	HA-HES	HES-HES	HA-nonHES	*p* value
InTEM				
Coagulation time (s)				
PreCPB	187 [173-224]	204 [148-289]	200 [172-271]	0.75
PostCPB	242 [187-268]	228 [162-283]	274 [219-344]	0.428
Clot formation time (s)				
PreCPB	91 [75-114]	88 [71-132]	70 [68-92]	0.124
PostCPB	115 [92-193]*	121 [80-208]	119 [101-138]*	0.972
α angle (°)				
PreCPB	73 [68-75]	73 [69-76]	76 [73-77]	0.109
PostCPB	72 [61-73]	70 [54-76]	69 [65-71]*	0.977
Maximum clot firmness (mm)				
PreCPB	60 [57-64]	63 [58-65]	61 [56-65]	0.602
PostCPB	54 [45-58]*	52 [45-56]*	57 [51-59]*	0.085
ExTEM				
Coagulation time (s)				
PreCPB	57 [49-75]	55 [49-67]	50 [45-52]	0.123
PostCPB	58 [50-80]	55 [45-70]	52 [45-60]	0.234
Clot formation time (s)				
PreCPB	104 [79-124]	99 [82-112]	85 [73-112]	0.514
PostCPB	114 [106-165]	105 [86-144]	120 [93-126]*	0.482
α angle (°)				
PreCPB	71 [65-74]	72 [68-74]	74 [71-78]	0.130
PostCPB	69 [64-72]	72 [67-76]	74 [70-76]	0.093
Maximum clot firmness (mm)				
PreCPB	59 [54-61]	63 [58-65]	62 [57-66]	0.057
PostCPB	56 [50-62]	59 [56-63]	58 [55-61]*	0.314
FibTEM				
Maximum clot firmness (mm)				
PreCPB	14 [11-17]	17 [14-25]	18 [15-20]	0.052
PostCPB	16 [13-20]	17 [11-20]	18 [15-25]	0.658

preCPB, before cardiopulmonary bypass; postCPB, after cardiopulmonary bypass; ROTEM, rotation thromboelastography; HA, 5% human albumin; HES, 6% hydroxyethyl starch 130/0.4; InTEM, intrinsic ROTEM; ExTEM, extrinsic ROTEM; FibTEM, fibrinogen ROTEM.
Values are median [interquartile range].
*$p<0.05$ between pre- and postCPB within group.

There were no significant differences in the serum concentrations of inflammatory markers among the groups throughout the study period. TNF-α, IL-6, and IL-8 were significantly increased in all groups throughout the postoperative period compared to their corresponding baseline values. TNF-α and IL-8 in all groups were highest 4 hours after CPB and decreased as time passed. IL-6 was highest 4 and 12 hours after CPB in all groups (Fig. 1).

DISCUSSION

This study evaluated the influence of 6% HES 130/0.4 on coagulation and inflammation, compared with human albumin when used for both CPB priming and perioperative fluid therapy in patients undergoing complex valvular heart surgery. No significant differences were noted based on the type of colloid used. Postoperative coagulation profiles evaluated with ROTEM demonstrated sporadic increases in clot formation time and coagulation time, without any differences in the actual amount of perioperative bleeding or transfusion requirements among the groups. Also, inflammatory markers showed significant activation after CPB without any differences among the groups.

Compared with its congeners, the lower molecular weight of 6% HES 130/0.4 (mean molecular weight: 130 kDa; degree of substitution: 0.4) has been shown to be associated with minimal coagulation disturbance,[7-9] while the lower

Table 3. Blood Loss, Transfusion Requirement, Coagulation Variables, and Fluid Balance

	Intraoperative	Postoperative 24 h
Blood loss (mL)		
HA-HES	500 [480-720]	450 [380-740]
HES-HES	583 [420-700]	495 [410-1220]
HA-nonHES	500 [485-665]	430 [280-685]
Transfused pRBC (units)/patients number (%)		
HA-HES	1 [0-1]/10 (56)	0 [0-1]/8 (44)
HES-HES	1 [0-2]/11 (61)	0 [0-1.5]/8 (44)
HA-nonHES	0 [0-1]/7 (39)	0 [0-1]/7 (39)
Transfused FFP (units)/patients number (%)		
HA-HES	0 [0-3]/5 (28)	0 [0-0]/3 (17)
HES-HES	0 [0-3]/5 (28)	0 [0-0.5]/4 (22)
HA-nonHES	0 [0-3]/5 (28)	0 [0-0]/3 (17)
Transfused Plts (units)/patients number (%)		
HA-HES	0 [0-0]/2 (11)	0 [0-0]/1 (6)
HES-HES	0 [0-0]/3 (17)	0 [0-0]/1 (6)
HA-nonHES	0 [0-0]/1 (6)	0 [0-0]/2 (11)
Hematocrit (%)		
HA-HES	36±6	27±2
HES-HES	36±6	29±4
HA-nonHES	36±4	30±3
Platelet count ($10^9 \cdot l^{-1}$)		
HA-HES	226±50	93±23
HES-HES	213±61	100±14
HA-nonHES	188±58	103±29
PT (s)		
HA-HES	12.8±3.0	14.1±1.9
HES-HES	13.7±5.6	13.6±1.3
HA-nonHES	13.8±3.3	14.1±1.9
aPTT (s)		
HA-HES	36.5±12.4	34.1±7.3
HES-HES	35.4±11.0	36.5±19.3
HA-nonHES	36.2±14.7	33.9±12.8
HES (mL)		
HA-HES	650 [500-1000]	550 [215-783]
HES-HES	1000 [1000-1400]	500 [200-800]
HA-nonHES	0 [0-0]*	0 [0-0]*
HA (mL)		
HA-HES	500 [500-500]	0 [0-0]
HES-HES	0 [0-0]†	0 [0-0]
HA-nonHES	500 [500-500]	0 [0-0]
Plasmalyte solution (mL)		
HA-HES	3000 [2450-3400]	3758 [2728-4665]
HES-HES	2498 [1953-2600]	3537 [3040-4341]
HA-nonHES	2403 [2055-3415]	3295 [2657-3933]

HA, 5% human albumin; HES, 6% hydroxyethyl starch 130/0.4; pRBC, packed red blood cells; FFP, fresh frozen plasma; Plt, platelet concentrations; PT, prothrombin time; aPTT, activated partial thromboplastin time.

Values are median [interquartile range] or mean±standard deviation or number of patients. Total, combined data of intraoperative and postoperative 24 h.

*$p<0.005$ compared with HA-HES and HES-HES group.

†$p<0.005$ compared with HA-HES and HA-nonHES group.

Table 4. Postoperative Datas

	HA-HES (n=18)	HES-HES (n=18)	HA-nonHES (n=18)	*p* value
Hemofiltration (mL)	1200 [800-1875]	1000 [850-2200]	1000 [100-1650]	0.417
AKI (n)	4	4	5	0.629
ICU day (day)	3.3±0.9	3.2±1.0	2.7±0.9	0.196
Hospital day (day)	13.2±4.4	11.2±5.5	12.4±3.4	0.671
Mortality (n)	0	1	0	0.981

HA, 5% human albumin; HES, 6% hydroxyethyl starch 130/0.4; AKI, acute kidney injury by RIFLE (R-risk, I-injury, F-failure, LE-loss and end stage renal disease) criteria; ICU, intensive care unit.
Values are number of patients or median [interquartile range].

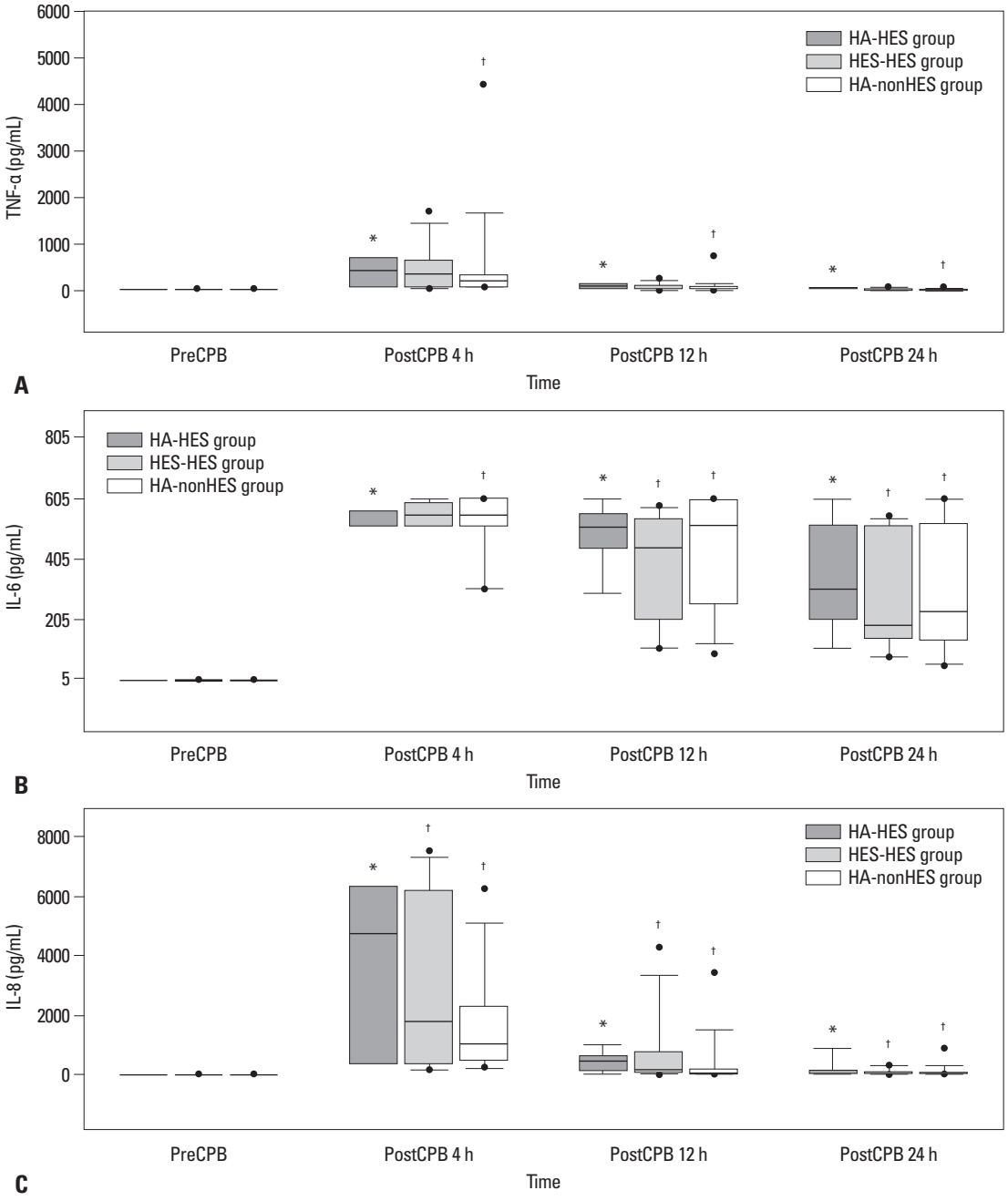

Fig. 1. Changes in inflammatory cytokines. (A) TNF-α, (B) IL-6, (C) IL-8. Data are expressed as median (maximum, minimum). *p<0.05, †p<0.005 compared with preCPB within group. HA, 5% human albumin; HES, 6% hydroxyethyl starch 130/0.4; CPB, cardiopulmonary bypass; TNF, tumor necrosis factor; IL, interleukin.

molecular substitution ratio has been shown to result in rapid total body clearance, potentially exerting less renal toxicity.[14] Nevertheless, concerns remain about the adverse effects of HES on hemostasis, especially in the cardiac surgical setting. HES may interfere with coagulation through reductions in factor VIII, von Willebrand factor, platelets, functional impairment of platelets, and enhancement of fibrinolysis.[15] However, some investigations have demonstrated that HES itself is not associated with clinically significant bleeding in defiance of its possible association with subclinical alterations of the coagulation system.[16]

CPB induces hemodilution, activation of the coagulation system, and fibrinolysis that negatively affects hemostasis.[1,17] Moreover, several studies have reported positive correlations between CPB duration and a negative influence on coagulation variables such as increased thrombin inhibition and fibrinolysis.[18] Indeed, coagulopathy and increased bleeding are serious complications, particularly occurring after prolonged CPB,[19,20] which is also associated with an increased risk of morbidity and mortality.[21,22] Yet, the safety and efficacy of 6% HES 130/0.4 in complex valvular heart surgery, in which prolonged duration of CPB is expected, remain elusive. Although the safety of 6% HES 130/0.4 as a component of the priming solution, compared with human albumin in terms of coagulation and inflammation, has been demonstrated in a recent study, that study was performed in patients undergoing simple mitral valvular surgery with a mean CPB duration of 1 h.[23] Moreover, no comprehensive data exist regarding the influence of 6% HES 130/0.4 on coagulation and inflammation when used as a perioperative fluid regimen.

In contrast to HES, albumin per se has no adverse influence on the coagulation system. The only adverse influence of human albumin on coagulation seems to stem from its subsequent hemodilutional effect.[2-4] Furthermore, when used for priming, albumin forms a layer on the surface of the CPB circuit, making it less thrombogenic, which decreases the affinity of the platelets, leading to their preservation.[24] In terms of inflammation, albumin has been shown to inhibit apoptosis[5] and attenuate the inflammatory response.[25] Nevertheless, its high cost and the possibility to transmit infection cannot be ignored.

In the current trial, perioperative use of up to 20 mL/kg 6% HES 130/0.4 for priming as well as perioperative fluid management yielded similar safety and efficacy results in terms of coagulation and inflammation when compared against human albumin. Regarding the routine coagulation tests, we could observe neither any differences among the groups nor within each group before and after CPB. Although CPB is known to exert adverse influence on the coagulation system, these findings are not surprising, since patients were transfused with FFP or platelet concentrates according to the results of these tests.

In contrast, a certain degree of sporadic deterioration of the coagulation system after CPB could be detected by ROTEM analysis without differences among the groups. ROTEM technology has the advantage of quickly providing a global assessment of coagulopathy, compared with the routine coagulation tests.[26-29] As our results indicate, no significant differences could be noted in the assessed ROTEM parameters among the groups despite sporadic deterioration of the coagulation system after CPB. In conjunction, no differences were noted in the actual amount of perioperative bleeding and transfusion requirement, confirming the safety of 6% HES 130/0.4 when used for priming and perioperative fluid therapy. The safety of 6% HES 130/0.4, compared to human albumin, is further confirmed by the findings that no differences could be noted when comparing with the albumin-nonHES group, in which HES was not administered at all.

As for the inflammation, we could observe a universal increase of the assessed markers, which peaked at 4 hours after CPB, as expected. However, as with ROTEM parameters, we could not observe any significant differences according to the type of colloid used. The inflammatory cytokines, including TNF-α, IL-6, and IL-8, have been shown to correlate with the severity of tissue damage induced by surgery and the inflammatory response to CPB.[30] Although albumin has been shown to modulate the ensuing CPB-related inflammation, evidence on the influence of other priming colloids on the inflammatory response is limited and inconclusive. As we could not observe any differences in the assessed inflammatory markers even in the albumin-nonHES group, the choice of priming solution and perioperative fluid does not seem to affect the inflammatory response following cardiac surgery using CPB.

Although not the primary endpoint of this study, we assessed the incidence of acute kidney injury, as concerns have been raised in recent literature on a potential adverse influence of HES solution on the renal function.[31,32] In contrast to those previous studies, we did not observe any negative effects of HES on the kidney when compared with albumin and plasmalyte solution, which may be attributable to the different patient population, type of HES solution

(10% versus 6%) and the total allowable volume of HES.[31,32] Nonetheless, it is beyond the scope of this study to validate the renal safety of 6% HES 130/0.4 as this study is not sufficiently powered to draw any conclusion in that regard, which merits further studies.

The limitations of this study are as follows. First, as we calculated the sample size on the basis of the previous study to address a difference in ROTEM variables, it is difficult to extrapolate the effects of different priming solutions and perioperative fluids on the actual clinical endpoints from the current small scale and a single-center study. Second, intraoperative blood loss during cardiac surgery is difficult to accurately assess. Although we had used the intraoperatively processed volume by a cell salvage device as a surrogate marker, actual amount of intraoperative blood loss may have been different. Third, ROTEM was performed 24 hours after CPB. The reason we did not perform the ROTEM analysis at the end of the surgery was that coagulation at this time point could be influenced by many factors including residual hemodilution, excess free water and heparin rebound. Although data at various time points postoperatively could be missed, sporadic deterioration of the coagulation system could still be depicted by ROTEM analysis 24 h after CPB as observed in the current study.

In conclusion, 6% HES 130/0.4, when used for priming and perioperative fluid therapy up to 20 mL/kg, seemed to yield similar influence on the ensuing coagulopathy and inflammatory response following complex valvular heart surgery requiring prolonged duration of CPB, compared with conventional fluid regimen including albumin and plasmalyte.

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